Cervical Priming Prior to Operative Hysteroscopy: a Randomized Clinical Trial Comparing Evening Primrose Oil Versus Dinoprostone Gel

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Objective: This study aimed to determine the efficacy of evening primrose oil versus dinoprostone gel as a cervical priming agent prior to operative hysteroscopy.
Methodology: Nine patients were randomized to receive either oral Evening Primrose Oil 1000mg/capsule one capsule three times a day for 7 days (n=4) versus 500 mcg intracervical dinoprostone gel 12 hours (n=5) prior to the procedure. The primary outcome measures were baseline cervical width prior to operative hysteroscopy. The secondary outcomes were surgeons' subjective assessments of insertion difficulty, number of patients requiring cervical dilatation, duration of cervical dilatation, pre-operative pain, adverse effects and complications.
Results: Both agents, Evening primrose oil and dinoprostone gel, were effective for cervical dilatation with a mean cervical diameter of 8.0 ± 1.4mm and 8.2 ± 1.3mm, respectively (P=0.832). There were no significant difference in the mean cervical diameter, ease of insertion of operative hysteroscope, time required for and number of patients requiring cervical dilatation. More patients in the dinoprostone complained of hypogastric pain prior to the procedure. No perioperative complications were observed in both groups.
Conclusion: Both oral Evening primrose oil and intracervical dinoprostone gel were equally effective in inducing proper cervical priming prior to operative hysteroscopy. Nevertheless, Evening primrose oil may be superior due to its oral route, reduced cost, patient convenience and acceptability.

Key words: evening primrose oil, dinoprostone gel, cervical priming, operative hysteroscopy

Introduction

Hysteroscopy is a valuable procedure in the minimally invasive management of patients with intrauterine abnormalities. Diagnostic hysteroscopy allows for a panoramic view of the uterine cavity while operative hysteroscopy offers a minimally invasive approach to the treatment of intrauterine lesions. These include hysteroscopic myomectomy, polypectomy, and hysteroscopic metroplasty. Well-known complications associated with hysteroscopy include cervical tears, bleeding, the creation of false tracts, and uterine perforation.[1]

Despite the fact that this procedure is widely used, one of the major problems of hysteroscopic surgery is difficulty in entering the internal cervical os with the outer sheath of the operative hysteroscope. Given that cervical dilatation may increase the procedure's complication rate, a method that could reduce the requirement of dilating the cervix would be of high clinical importance. Cervical priming would have a central role in facilitating the procedure.[2] Cervical priming refers to softening of the cervix by mechanical or medical means prior to an intervention.[3] Softening of the cervical tissue is a process involving inflammatory reactions.[4]

Traditional cervical dilatation using Hegar's dilators may not be feasible in some patients with very tight cervix or cervical abnormalities. So a variety of mechanical and pharmacologic agents have been used to effect cervical change prior to hysteroscopy.

An example of mechanical agent is the laminaria tent. It is made from stems of Laminaria japonica (brown sea weed) and in its dry form, it absorbs fluid from the cervix facilitating cervical dilatation. Vaginal insertion of laminaria has been shown to be effective in priming the cervix with minimal local and no systemic side effects. However, it is costly and not readily available. Although cervical dilatation is achieved by the use of laminaria, the consistency of the cervix is still firm, compromising the ease of the procedure.[5]

Prostaglandins have been used for cervical ripening prior to hysteroscopy since 1985. In other countries, misoprostol, a prostaglandin E1 analog initially designed for the treatment of peptic ulcers has been successfully used as a cervical ripening agent both in obstetric (medical abortion, induction of labor and treatment of postpartum hemorrhage) and gynecologic procedure (operative hysteroscopy).[6,7,8] It can be administered orally, intracervically or intravaginally, but the latter is more effective according to several clinical studies. It is widely used due to its easy application, reduced cost and patient convenience. However, in the Philippines, misoprostol has been cited as an abortive drug and cannot be used for obstetric and gynecologic indications as per Philippine FDA and Housebill No 2043.[9]

Another prostaglandin used for cervical priming is the topically administered prostaglandin E2 (dinoprostone) which was initially used for labor induction in unfavorable cervices. It works by initiating collagen degradation as a response to the collagenase secretion it induces. In one recent local study, it demonstrated that dinoprostone E2 gel was effective as a cervical priming agent. It decreased cervical resistance, reduced the need for further cervical dilatation in some, facilitated further cervical dilatation in others and eased the performance of the hysteroscopic procedure as a whole. There is also a tendency towards minimizing iatrogenic cervical or uterine injuries with mechanical dilatation. Its use, however, was associated with preoperative vaginal bleeding and hypogastric pain[10]. Presently, it is the only agent approved for preinduction cervical ripening.

An alternative pharmacologic cervical priming agent is Evening primrose oil. It is a standardized extract obtained from the seeds of the plant Oenothera biennis.[5] It is in the form of soft gel capsule. It contains an omega-6 essential fatty acid, gamma-linoleic acid (GLA), which is believed to be the active ingredient. Essential fatty acids magnetize oxygen as well as produce electrical currents. Once in the body, amino acids and essential amino acids are transformed into hormone-like substances called prostaglandins, which causes allergic response and inflammation. In another local study, it was shown to be an acceptable alternative cervical priming agent; however 47.62% of patients given this drug 1000 mg TID orally for 7 days prior to hysteroscopy still required dilatation.[5]

Although safer and more convenient methods of cervical priming are being utilized, presently, there is no standard for cervical priming in patients for hysteroscopy.

So far, there have been no comparative studies done on the efficacy of the two pharmacologic agents (Evening Primrose oil and Dinoprostone gel) available in the Philippines for cervical priming prior to hysteroscopy.

Significance of the Study

This study aims to compare the efficacy of oral Evening primrose oil versus intracervical Dinoprostone gel as a cervical priming agent in an effort to prevent complications associated with operative hysteroscopy.

Objective of the Study

General Objective

To determine the efficacy of Evening primrose oil versus Dinoprostone gel as a cervical priming agent when used prior to operative hysteroscopy.

Specific Objectives

1. To determine the efficacy of oral Evening primrose oil versus intracervical Dinoprostone gel as a cervical priming agent prior to hysteroscopy with respect to the following:
   a. Initial cervical dilatation prior to hysteroscopy (mm)
   b. Number of patients requiring cervical dilatation

2. To determine efficacy of oral Evening primrose oil versus intracervical Dinoprostone gel as a cervical priming agent with respect to the following technical characteristics:
   a. Subjective ease of cervical dilatation (as determined by the Likert scale)
   b. Duration of cervical dilatation to Hegar size 9 (seconds)

3. To compare the following pre and post-operative characteristics of the patients given oral Evening primrose oil versus intracervical Dinoprostone gel:
   Pre-operative:
   a. Pre-operative pain assessment (VAS score)
   b. Adverse events (vaginal bleeding, diarrhea)
   c. Cost
   d. Patient's preference regarding route of administration

Post-operative:

a. Complications associated with the procedure

Materials and Methods

Study Design

This study was approved by the ethics review board of the institution. The study design was a randomized clinical trial that compared oral Evening primrose oil versus intracervical Dinoprostone gel as a cervical priming agent. Surgeons were blinded to the treatment allocation. This was conducted from July 2012 to August 2012 in the Section of Reproductive Endocrinology and Infertility and Menopause, Department of Obstetrics and Gynecology of our institution.

Patient Population

Patients who underwent operative hysteroscopic surgeries for intrauterine lesions diagnosed by saline infusion sonography done on day 8 to day 10 of menstruation at our institution were included in the study. The principal investigator was the one who recruited the patients and the recruitment was done in the Reproductive Endocrinology and Infertility office.

Reasons for exclusion were the following: pregnant patients, lactating women, mentally disadvantaged women, patients 18 years old and below, genital tract infection, dilated cervix due to a prolapsed intrauterine lesion, patients with mullerian anomalies, history of cervical incompetence or any major uterine or cervical surgery, previous treatment with gonadotropin releasing hormone (GnRH) agonist, known hypersensitivity and contraindication to the cervical priming agents (for Evening primrose oil - patients with diabetes mellitus, liver and renal disease while for prostaglandins (Dinoprostone gel) – patient with history of asthma, glaucoma, or preexisting cardiac or cardiovascular disease – were not included in the study as well. Patients who did not give their consent to be part of the study were also excluded. All eligible patients were admitted a day before the operation after a detailed history taking and clinical examination. Routine baseline laboratory examinations were performed. They were discharged the following day and asked to follow up one week after the operation.

Sample Size

Computation based on the percentage of doctors who agreed with the ease of insertion of hysteroscope.

1. 95% confidence level
2. 80% power to detect a difference
3. 19% agree in the evening primrose study (Capco and Tanangonan[7]) and 62% in the dinoprostone group (Limson and Oblepias[10]), for a difference of 43%
4. 1:1 ratio

N= [1.96 x sqrt (pmean qmean) + 0.843 x sqrt (p1q1 + p2q2)]sq/ (diff)sq

N= [1.96 x sqrt(.405 x .595) + 0.843 x sqrt (.19 x .81) + (.62 x 0.38)]sq / .43sq

N= 12/group

Methods

Out-patient medical records of women presenting with intrauterine lesions diagnosed by saline infusion sonography done on day 8 to day 10 of menstruation were screened for eligibility to participate in the trial. Candidates for the trial were approached by the fellow of the Department of Obstetrics and Gynecology and were given information regarding the study. A detailed history and thorough physical examination were done on prospective participants. Risks associated with the procedure (hysteroscopy) were discussed with the patient as usually practiced in such admissions. Patient were also given information regarding the products (Evening primrose oil and Dinoprostone E2 gel); its label use; benefits and potential side effects. After informed consent was obtained, the subjects were randomized using a table of computer generated random numbers. The number corresponded to sealed envelopes that indicated whether Drug A or Drug B should be given.

Patients included in this study were randomized into 2 groups: Group A received oral Evening primrose oil 1000mg 1 capsule three (3) times a day for 7 days prior to hysteroscopy. Group B on the other hand was given 500mcg Dinoprostone gel, a gel applied intracervically by the physician-in-charge 12 hours prior to the surgery. Patients remained supine for at least 30 minutes after the Dinoprostone gel administration.

Operative hysteroscopy was performed by any one of the three senior fellows of the Endoscopic Unit with comparable level of experience. Each of them has done at least eight (8) hysteroscopic procedures prior to this study. All the hysteroscopic procedures were decked equally among those three senior fellows so not one surgeon performed all the procedures. A standard rigid hysteroscope with a 9mm outer sheath diameter was used. Surgery in premenopausal patients was timed during the proliferative phase of the cycle. Prior to the hysteroscopy, a size 1 Hegar dilator was inserted through the internal os, then followed by successively larger Hegar dilators until

resistance was met. The size of the largest Hegar dilator used before subjective resistance was felt by the surgeon was noted as the preoperative degree of dilatation. This was reflective of the ease of cervical dilatation, which was the primary outcome measured in this study.

Outcome Measures

Primary outcome as stated above was the cervical dilatation in millimeters prior to hysteroscopy as measured by the maximum caliber Hegar dilator that could be inserted into the cervix without resistance. A 30 degree hysteroscope with a 9 millimeter operative implement was used.

Secondary outcomes included number of patients requiring cervical dilatation, subjective ease of cervical dilatation recorded on a Likert scale as assessed by the surgeon and duration of cervical dilatation to Hegar dilator size 9 (size of the operative hysterscope) and the time needed to finish the surgery were recorded. Further data that were recorded were the complications related to cervical dilatation and hysteroscopic surgery, and associated peri-operative side effects and complications of the cervical ripening agent. Data such as age, parity and menopausal status were also recorded.

Statistical Analysis

Demographic and clinical characteristics were described [mean, standard deviation (SD) and minimum-maximum values were reported for categorical variables] according to the treatment group. Independent t-test was used to test the null hypothesis that there was no difference between the Evening primrose oil and placebo against the alternative that there was a difference for the following variables: 1) initial cervical dilatation, 2) subjective ease of cervical dilatation, 3) duration of cervical dilatation, and 4) pre-operative pain measured by Visual Analog Scale. Likewise, the 95% confidence intervals of the differences between the two groups with respect to these variables were analyzed using the student's t-test for continuous variables and chi-square for categorical variables. For all tests, a 95% confidence level was considered significant.

Results

A total of 15 patients were screened for eligibility. Six patients were excluded: 5 due to their prolapsed intrauterine lesion while the other one refused to participate in the study. Nine patients were included and randomized, 4 in the Evening primrose oil group and 5 in the Dinoprostone gel. The two groups are comparable or are essentially similar in their demographic characteristics - age, parity, menopausal status (Table I). The clinical parameters of women receiving Evening primrose oil and Dinoprostone gel were shown in Table 1 as well. There was no statistically significant difference between the two groups with respect to indications, the most common of which were endometrial polyps followed by myoma and retained intrauterine device (IUD), type of surgery and anesthesia given for operative hysteroscopy.

Table 2 demonstrates the technical characteristics of both groups. The mean initial cervical dilatation prior to hysteroscopy for both the Evening primrose oil group and Dinoprostone gel group was 8-8.2 cm (8.0±1.4 mm and 8.2 ± 1.3 mm respectively, with a P value of 0.832) This was not statistically significant. Four patients (two in each group), required cervical dilatation prior to hysteroscopy which was also not statistically significant. Aside from these, the duration of cervical dilatation (11.5 ± 13.304 and 21.6± 37.674 minutes respectively, P value of 21.6± 37.674) and duration of hysteroscopy procedure (52.5 ± 38.837 and 46.0 ± 28.809 minutes respectively, (P=0.780) were statistically not significantly different in both treatment groups.

Patients in the Dinoprostone gel group experienced more severe pain, from mild to intense pain, preoperatively, than those in the Evening primrose group with no complaint of pain at all. (Table 3). This was evident in Table 4 where it showed that the difference was highly significant (P=0.0079). Post-operatively, all subjects in both groups did not experience any complications such as cervical tear, uterine perforation nor false tract.

Accumulated points per patient based on Likert scale as assessed by the surgeons did not differ significantly between the two groups, P value of 0.1667 (Table 5). Evening primrose oil and dinoprostone gel were assessed as equally good in terms of easy insertion of dilators, use of less force, less time needed in dilating the cervix to Hegar size 9, easy maneuvering of the hysteroscope and providing less trauma to the cervix (Table 6).

Table 7 shows that most of the patients favor Evening primrose oil (n= 6) over Dinoprostone (n=3) due to its cheaper cost. Its oral route of administration (n=5) is more acceptable compared to the intracervical application of Dinoprostone gel (n=4).

Discussion

This was the first prospective randomized clinical trial to compare the effectiveness of oral Evening primrose oil versus Dinoprostone intracervical gel for cervical priming

Table 1. Demographic and clinical characteristics of the patients according to treatment groups.

Characteristics	Primrose Oil Group (n=4)	Dinoprostone Gel Group (n=5)	P value
Age in years			
Mean (SD)	44.5 ± 11.818	34.8 ± 9.149	0.207
Min-max	32-60	24-47	(-6.728 to 26.128)
Parity			
Nullipara	0	1	0.524
Primipara	1	2	
Multipara	3	2	
Menopausal Status			
Premenopausal	3	5	0.444
Postmenopausal	1	0	(RR=0.153 to 0.917)
Indications for Hysteroscopy			
Endometrial polyp	3	2	0.524
Submucous myoma	1	1	
Thickened endometrium	0	0	
Retained/displaced IUD	0	2	
Hysteroscopic Procedures			
Polypectomy	3	2	0.524
Myomectomy	1	1	
Targeted endometrial biopsy	0	0	
Removal of IUD	0	2	
Type of Anesthesia Used			
Spinal	4	5	1.00
General	0	0	

Table 2. Technical characteristics of the patients according to treatment groups.

Characteristics	Primrose Oil Group (n=4)	Dinoprostone Gel Group (n=5)	P value	Difference (95% confidence interval)
Initial cervical dilatation prior to hysteroscopy (mm)				
Mean (SD)	8.0 ± 1.414	8.2 ± 1.304	0.832	-2.341 to + 1.941
Min-max	6-9	6-9		
Patients requiring cervical dilatation, n (%)	2	2	1.00	—
Duration of cervical dilatation (in seconds)				
Mean (SD)	11.5 ± 13.304	21.6 ± 37.674	0.626	-57.247 to + 37.047
Min-max	0-24	0-87		
Duration of hysteroscopy procedure (minutes)	52.5 ± 38.837	46.0 ± 28.809	0.780	-46.498 to + 59.498

Table 3. Comparison of the two groups with respect to pre-operative pain.

Pre-operative Pain (Visual Analog Scale 0-1)	Evening Primrose oil Group (n=4)	Dinoprostone Gel Group (n=5)
0	4	0
1-3	0	3
4-6	0	1
7-10	0	1

P=0.0079

Table 4. Comparison of pre-operative and post-operative side effects of evening primrose oil and dinoprostone gel.

Side Effects	Evening Primrose Oil (n=4)	Dinoprostone Gel (n=5)	P value	Difference (95% confidence interval)
Pre-operative				
None	4	0	0.0079	--
Hypogastric pain	0	5		
Vaginal bleeding	0	0		
Diarrhea	0	0		
Post-operative				
None	4	5	1.00	-
Cervical tear	-	-		
Uterine perforation	-	-		
False tract	-	-		

Table 5. Accumulated points per patient based on the Likert scale, as assessed by the surgeons.

	Evening Primrose Oil (n=4)	Dinoprostone Gel (n=5)
<10 strongly disagree	0	0
10-15 disagree	0	0
16-20 neither agree or disagree	2	0
21-25 agree	2	5

P=0.1667 RR= 1.08 to 11.292

Table 6. Comparison of assessment of surgeons (based on the Likert scale) between dinoprostone and control group.

Side Effects	Evening Primrose Oil (n=4)		Dinoprostone Gel (n=5)		P value	Difference (95% confidence interval)
	Mean	Standard deviation	Mean	Standard deviation		
Easy insertion of Hegar dilators until resistance	4.75	0.500	5	0	0.391	-0.500 to +0.545
Less force was used in dilating the cervix	4.75	0.500	5	0	0.391	-0.500 to +0.545
Less time was needed to dilate the cervix to Hegar size 9	4.75	0.500	5	0	0.391	-0.500 to +0.545
Easy maneuvering of hysteroscope during procedure	4.25	0.957	4.8	0.447	0.288	-1.677 to +0.577
Cervix was not traumatized during the procedure	4.5	0.577	5	0	0.182	-1.418 to + 0.418

1= strongly disagree
2= disagree
3= neither agree nor disagree
4= agree
5= strongly agree

Table 7. Comparison of the two groups with respect to cost and route of administration.

	Evening Primrose Oil	Dinoprostone Gel
Favors the cost of the agent	6	3
Favors the route of administration of the agent	5	4

prior to operative hysteroscopy. Our results showed that both were effective in dilating the cervix with a mean baseline cervical dilatation of 8.0 ± 1.414mm and 8.2 ±1.304mm, respectively. There was no significant difference between the two priming agents with regard to the proportion of patients requiring cervical dilatation, duration of cervical dilatation and duration of hysteroscopy procedure.

Many patients require cervical dilatation prior to operative hysteroscopy. This depends on the size of the instrument used for the operation. An operative hysteroscope/resectoscope typically has a diameter of 10 mm which is used to treat endometrial pathology. In women with a firmly closed and rigid cervix, dilatation can lead to considerable traumatization of the tissue. Furthermore, complicated cervical dilatation is attended by the risk of lacerations caused by the tenaculum, the creation of false passages and an increased risk of uterine perforation[4].

The uterine cervix is essentially a connective tissue organ. Smooth muscle cells account for less that 8% of the distal part of the cervix. Collagen types I and III constitute the most abundant extracellular matrix proteins in the human uterine cervix[11] The exact mechanism leading to physiological cervical ripening or softening is not known. The biochemical events that have been implicated in cervical ripening are 1) a decrease in total collagen content, 2) an increase in collagen solubility, and 3) an increase in collagenolytic activity[11]. The biochemical changes were described as similar to an inflammatory response. Indeed, during cervical ripening there is an influx of inflammatory cells into the cervical stroma, which increases matrix metalloproteinases and thereby leads to the degradation of collagen and cervical softening .

A naturally occurring prostaglandin produced by the cervix is dinoprostone. It induces enzymatic changes that causes breakdown and reduction of collagen concentration, as well as an increase in both glycosaminoglycans and cervical water content; all these cause cervical softening. Cervical changes were noted to start within 5 hours and were completed in 12 hours after application of the gel. Although Evening primrose oil is an amino acid. Once it is inside the body, essential amino acids are transformed into hormone-like substances called prostaglandins, like Dinoprostone, which induces allergic response and inflammation. Therefore, both Evening primrose oil and Dinoprostone gel can be used to ripen the cervix, resulting in a softer, more easily dilated cervical canal, which in turn can decrease the number of women who require further mechanical cervical dilation before surgery.

There was a no significant difference between oral Evening primrose oil and intracervical Dinoprostone gel with regard to insertion difficulty and doctors' satisfaction with the procedure based on the Likert scale wherein both agents were assessed as equally good in terms of easy insertion of dilators, use of less force, less time needed in dilating the cervix, easy maneuvering of the operative hysteroscope, and providing less trauma to the cervix.

There was no significant effect of the type of anesthesia used on the cervical dilatation since all patients were given spinal anesthesia. Choice of anesthesia depends on several factors including the procedure, the facility, the surgeon's experience and preference, the hysteroscopy equipment and patients factors[5]. Spinal and general anesthesia can be equally effective. Since the effect of general anesthesia can easily wean off, it may result to shorter hospital stay thus less hospital cost. Spinal anesthesia, on the other hand, is associated with increased recovery time due to prolonged motor sensory block.

Patients in the dinoprostone group complained of more severe hypogastric pain preoperatively compared to Evening primrose oil group. The hypogastric pain is secondary to the myometrial stimulation caused by the prostaglandin[12]. Despite experiencing hypogastric pain, four (4) patients still preferred the intracervical insertion of dinoprostone 12 hours prior to the operation than taking the oral Evening primrose oil 3 times a day for 7 days. This is attributed to the compliance in completing the dose of the oral Evening primrose oil. The only drawback to the use of Dinoprostone gel is its cost. One pre-filled gel costs Php959.00 compared to Php483.00, equivalent to 21 softgel capsules - Php23.00/soft gel capsule 3 times a day for 7 days. Its application also needs a trained personnel to administer it. Evening primrose oil, thus, has the advantage over Dinoprostone in terms of its cost, oral route, patient acceptability and convenience since it can be taken at home.

In our study, no perioperative complications such as cervical tear, uterine perforation and false tract nor adverse events were encountered in both groups compared to previous study (Limson and Oblepias, 2011) where they had 3 postoperative complications such as cervical tear and uterine perforation.

A potential weakness of this study is that the same surgeon did not perform all the procedures and that the resistance during cervical dilatation was assessed subjectively. This may introduce the potential for bias because each clinician may have a different perception of cervical resistance. To overcome this drawback, a tensinometer/tonometer may be used to measure the force applied during cervical dilatation[4,13]. However, this is not available in our institution.

Conclusion

From this study, it is concluded that both oral Evening primrose oil and intracervical Dinoprostone gel were shown to be effective in inducing adequate cervical priming prior to operative hysteroscopy with minimal time of cervical dilatation. Both agents were also acceptable to the surgeons as measured by the Likert scale. Nevertheless, Evening primrose oil is superior as it has the following advantages: oral route, cheaper price and patient convenience and acceptability.

Further studies with a sufficient number of trial participants are required in order to validate the results of our study regarding the use of Evening primrose oil and Dinoprostone gel as cervical priming agents prior to operative hysteroscopy.

Disclosure of Interest

No potential conflict of interest was reported by any of the authors.

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